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(54) Use of R-Fluoxetine as selective serotonin IC-receptor ligands.

(57) The present invention provides a method of employing (R)-fluoxetine to treat conditions related to the selective occupation of 5HT_{1C} receptors.

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This invention relates to the discovery that the (R)-enantiomer of fluoxetine selectively occupies the serotonin 1C receptor.

During the past decade, the relationship between monoamine uptake and a variety of diseases and conditions has been appreciated and investigated. For example, the hydrochloride salt of fluoxetine (dl-N-methyl-3-[4-(trifluoromethyl)phenoxy]-3-phenylpropylamine) is a selective serotonin (5-hydroxytryptamine, 5HT) uptake inhibitor. Fluoxetine hydrochloride is marketed under the trademark PROZAC® for the treatment of depression. This compound is among many taught in U.S. Patents Number 4,018,895, 4,194,009, and 4,314,081 as being potent, selective blockers of serotonin uptake.

Fluoxetine is a racemate of the two enantiomeric forms. The biological and pharmacological activity of each enantiomer as 5HT uptake inhibitors has been reported to be essentially the same; see, Robertson *et al.*, *J. Med. Chem.*, **31**, 1412 (1988) and references cited therein.

This invention provides a method for treating a mammal suffering from or susceptible to a condition which can be improved or prevented by selective occupation of the 5HT_{1C} receptor which comprises administering (R)-fluoxetine, or a pharmaceutically acceptable salt or solvate thereof, to said mammal. or a pharmaceutically acceptable salt or solvate thereof.

This invention includes the use of pharmaceutically acceptable salts of (R)-fluoxetine. Since (R)-fluoxetine is an amine, it is basic in nature and accordingly reacts with any number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, parabromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonates, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, hippurate, gluconate, lactobionate, and the like salts. Preferred pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as fumaric acid and maleic acid.

The pharmaceutically acceptable salts of (R)-fluoxetine can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

(R)-Fluoxetine can be prepared by any of a number of methods generally known in the art. For example, there are several methods provided in the literature for making the racemate of fluoxetine, which, in turn can be resolved into its (S) and (R) components by standard methods.

Thus, (R)-fluoxetine can be prepared as reported by Robertson, *et al.*, *J. Med. Chem.*, **31**, 1412 (1988).

Alternatively, (R)-fluoxetine can be synthesized by the same methods as reported for preparing racemic fluoxetine employing chiral starting materials.

The particular dose of compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case, including the route of administration, the particular condition being treated, and similar considerations. (R)-Fluoxetine can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes. A typical daily dose will contain from about 0.01 mg/kg to about 20 mg/kg of (R)-fluoxetine. Preferred daily doses will be about 0.05 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg.

(R)-Fluoxetine has the ability to treat a variety of disorders in mammals associated with dysfunction in serotonergic systems involving the 1C receptor such as obesity, bulimia, alcoholism, pain, sleep apnea, obsessive-compulsive disorders, substance abuse (eg, cocaine, heroin, amphetamines, etc.), and migraine.

The following experiment was conducted to demonstrate the ability of (R)-fluoxetine to affect radioligand binding to five subtypes of serotonin receptors. This general procedure is set forth by Wong *et al.*, *Life Sciences*, **46**, 231 (1990).

Bovine choroid plexus and brain tissues from male Sprague-Dawley rats was homogenized in 9 volumes of 0.32 M sucrose. After centrifugation at 1000 x g for 10 minutes and then at 17,000 x g for 20 minutes, a crude synaptosomal fraction was sedimented. The pellet was suspended in 100 volumes of 50 mM Tris-HCl, pH 7.4, incubated at 37°C for 10 minutes, and centrifuged at 50,000 x g for 10 minutes. The process was repeated, and the final pellet of membrane was suspended in ice-chilled 50 mM Tris-HCl buffer, pH 7.4.

Binding of ^3H -mesulergine to the $5\text{HT}_1\text{C}$ receptor and other serotonergic ^3H -ligands to subtypes of 5HT receptors (^3H -8-hydroxy-2-(di-n-propylamino)tetralin to $5\text{HT}_1\text{A}$; ^3H -serotonin to $5\text{HT}_1\text{B}$ and $5\text{HT}_1\text{D}$; ^3H -ketanserin to 5HT_2 ; and ^3H -1-methyl-N-(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)-1H-indazole-3-carboxamide to 5HT_3 receptors) was performed according to the method described in the above reference.

Briefly, membranes isolated from bovine choroid plexus (for $5\text{HT}_1\text{C}$) or rat brain were incubated at 25°C for 30 minutes in 2 ml of 50 mM Tris-HCl, pH 7.4; 10 mM pargyline, 0.6 mM ascorbic acid; 5 mM CaCl_2 ; and 2 nM ^3H -mesulergine or other tritiated ligand. Binding was terminated by filtering samples under reduced pressure through glass fiber (GFB) filters. The filters were washed 3 times with 5 ml of ice cold buffer and placed in scintillation vials with 10 ml of PCS (Amersham/Searle) scintillation fluid. Radioactivity was measured with a liquid scintillation spectrometer. Serotonin at 10 μM also included in separate samples to determine specific binding, which accounted for 90-70 percent of total binding.

The results of the evaluation of (R)-fluoxetine from these experiments are set forth below in Table I. In the Table, columns 2-6 provide the micromolar (μM) concentration of the test compound needed to inhibit radioligand binding by 50% for each of the indicated receptors.

Table I

AFFINITIES OF (R)-FLUOXETINE FOR
SUBTYPES OF SEROTONIN RECEPTORS

Inhibition of Radioligand Binding to 5HT Receptor*

Compound	1A	1B	1C**	1D	2	3
(R)-fluoxetine	23	22	0.19	71	3.1	16

* IC_{50} IN μM (MICROMOLAR OR 10^{-6}M)

** Mean of three experiments

The compound and salts employed in the present invention are preferably formulated prior to administration. These pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. The active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 20 to about 80 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each

unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

5 **Claims**

1. A process for preparing a pharmaceutical formulation for the treatment of a mammal suffering from or susceptible to a condition which can be improved or prevented by selective occupation of the 5HT_{1C} receptor which comprises admixing (R)-fluoxetine, or a pharmaceutically acceptable salt or solvate thereof, with one
10 more more pharmaceutically acceptable carriers, diluents or excipients therefor.
2. The use of (R)- fluoxetine, or a pharmaceutically-acceptable salt or solvate thereof, for the preparation of a medicament for treating a mammal suffering from or susceptible to a condition which can be improved or prevented by selective occupation of the 5HT_{1C} receptor.
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3. A pharmaceutical formulation adapted for the treatment of a mammal suffering from or susceptible to a condition which can be improved or prevented by selective occupation of the 5HT_{1C} receptor comprising (R)-fluoxetine, or a pharmaceutically acceptable salt or solvent thereof, and one or more pharmaceutically acceptable carriers, diluents or excipients therefor.
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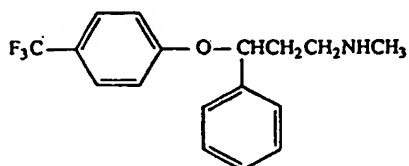
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⑤④ Use of R-Fluoxetine as selective serotonin 1C-receptor ligands.

⑤⑦ The present invention provides a method of employing (R)-fluoxetine to treat conditions related to the selective occupation of 5HT_{1C} receptors.



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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X,Y	PSYCHOPHARMACOLOGY, vol. 99, no. 2, 1989, pages 196-201, Springer-Verlag; J.C. NEILL et al.: "Selective reduction by serotonergic agents of hypertonic saline consumption in rats: evidence for possible 5-HT _{1c} receptor mediation" * Whole article *	1-3	A 61 K 31/135
Y	US-A-4 868 344 (H.C. BROWN et al.) * Whole document *	1-3	
Y	WO-A-8 903 692 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) * Whole document, espec. pages 3-7,10-11,15; example II *	1-3	
Y	J. MED. CHEM., vol. 31, no. 7, 1988, pages 1412-1417, American Chemical Society; D.W. ROBERTSON et al.: "Absolute configurations and pharmacological activities of the optical isomers of fluoxetine, a selective serotonin-uptake inhibitor" * Whole article *	1-3	
T	NEUROPSYCHOPHARMACOLOGY, vol. 5, no. 1, August 1991, pages 43-47, Elsevier Science Publishing Co., Inc.; D.T. WONG et al.: "Affinities of fluoxetine, its enantiomers, and other inhibitors of serotonin uptake for subtypes of serotonin receptors" * Whole document *	1-3	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 20-11-1991	Examiner GAC G.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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